

Applicants respectfully submit that entry of this Amendment is proper under 37 C.F.R. § 1.116 since this Amendment: (a) does not raise any new issue regarding further search and/or consideration since it clarifies issues already discussed in the prosecution and in the Personal Interview; (b) does not present any additional claims; and (c) places the application in better form for appeal, should an appeal be necessary. Entry of the Amendment is thus respectfully requested. Accordingly, reconsideration of the application in view of the following remarks is respectfully requested.

During the Personal Interview of October 22, 2002, it was brought to the Examiner's attention that there is a difference between affinity and thermostability and that there is no direct relationship between these two properties. This is because the thermostability for the lambda CI857 repressor is caused by a mutation in the hydrophilic domain, which is not directly involved in the DNA binding. Therefore, the affinity of the lambda CI857 remains the same. However, due to a conformational shift at temperatures higher than 30°C, the repressor dissociates from the DNA operator sequence. Surprisingly, mutations in the DNA operator sequence results in an increased thermostability of the thermosensitive repressor protein. Therefore, it was agreed that the teachings of the primary references, Pakula and Chen, (as well as the remaining cited references) did not apply to the present invention as the cited combination of references depended upon a mutation of the repressor protein, rather than the DNA of the operator. Additionally, it was agreed that the remaining references did not address the deficiency of the primary references to address the mutation of operators rather than repressors. Therefore, it was agreed that the obviousness rejections should be withdrawn.

The Examiner has requested new drawings in the present case. Applicant is in the process of preparing the new drawings and they will be submitted shortly. Therefore, it is requested that this objection be placed in abeyance until receipt of the corrected drawings.

Claim 47 has been objected to as duplicative of the range limitation included in Claim 46. Therefore, Applicant has adopted the Examiner's suggestion and cancelled Claim 47. It is requested that the objection be withdrawn.

Claims 38, 46, 69, and 70 have been rejected under 35 U.S.C. 112, first and second paragraphs, as not supported by adequate written description and indefinite, respectively. These claims have been rejected for reciting the term "non-naturally occurring." Claims 38, 46, 39, and 70 have been amended to remove the offending term, as the rejections under 35 U.S.C. 103 have been withdrawn (see discussion below). Therefore, it is requested that these rejections be withdrawn in light of the amendments made to the claims.

Claims 46-48, 50-62, 66-70, and 73-76 have been rejected under 35 U.S.C. 103(a) as obvious over the Chen reference in view of Eliason, Pakula, Benson, the '678 patent, and the '190 patent. As stated above, it was agreed during the personal interview of October 22, 2002 that this rejection would be withdrawn in light of the arguments presented therein, and summarized above. Therefore, it is requested that this rejection be withdrawn.

Claims 38-48, 50-62, 66-70 and 73-76 have been rejected under 35 U.S.C. 103(a) as obvious over the Chen reference in view of Eliason, Pakula, Benson, the '678 patent, the '190 patent, and the '093 patent. As stated above, it was agreed during the

personal interview of October 22, 2002 that this rejection would be withdrawn in light of the arguments presented therein, and summarized above. Therefore, it is requested that this rejection be withdrawn.

Claims 38-48 and 50-76 have been rejected under 35 U.S.C. 103(a) as obvious over the Chen reference with Eliason, Pakula, Benson, the '678 patent, the '190 patent, and the Szostak reference. As stated above, it was agreed during the personal interview of October 22, 2002 that this rejection would be withdrawn in light of the arguments presented therein, and summarized above. Therefore, it is requested that this rejection be withdrawn.

During the personal interview of October 22, 2002, the Examiner indicated that Claims 69 and 70 may be allowable if the limitations of Claims 66-68 were incorporated into Claims 69 and 70. Applicant has cancelled Claims 66-67 and incorporated their limitations into Claims 69 and 70. Additionally, Claim 68 has been cancelled and redrafted as Claims 77-78, which are dependent upon Claims 69 and 70. Therefore, it is requested that the application be allowed in light of these amendments.

It was also briefly questioned during the personal interview of October 22, 2002 whether the specification of the present application contains adequate written description to support the sequence claims (as opposed to the method claims). The Examiner indicated that he wished to review the claims. It is submitted that a rejection under this basis would not be proper.

Section 2163 of the MPEP discusses the written description requirement. It is noted that section 2163(I) states that "[t]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one

skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.” Section 2163(l) also states that “[a]n applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention.” Additionally, section 2163(l)(A) states that “[t]he claimed invention as a whole may not be adequately described where an invention is described solely in terms of its making coupled with its function and there is no described or art-recognized relationship between the structure of the invention and its function.” It is submitted that the present specification meets these requirements.

The specification provides extensive discussion of the methods used to determine and locate the sequences suitable for use in the claimed invention (see, for example, Example 1 in which the process of mutagenesis is described, as well as the process of verifying the mutation to obtain the presently claimed sequences). Additionally, the specification describes the limitations the claimed sequence must possess (see, for example, page 2, 3rd paragraph, and page 5, 3rd paragraph, to page 7, 1st paragraph). Additionally, the specification lists a specific example of the invention on page 7, 1st paragraph (the lambda operator sequence shown in SEQ ID NO.2). Also, page 6, 3rd paragraph, discloses that variants of SEQ ID NO. 1 and SEQ ID NO.3 are also encompassed by the claims. Furthermore, it is submitted that there is clear written description in the specification for the processes that may be used to produce the claimed sequences. Finally, the original claims (i.e., Claim 9), which are part of the original disclosure, fully disclose all elements of the sequence claims.

As a sample sequence is disclosed in the specification, it is submitted that a written description rejection would be improper because the existence of such a working example demonstrates that the applicant possessed the invention at the time of filing. Further, the fact that SEQ ID NO.2 was obtained through the use of the methods described in the present invention (as demonstrated by the language "according to the invention") proves that the methods disclosed in the specification would be sufficient for one of ordinary skill to produce and use the invention. Section 2163(I) only requires the description show that one of ordinary skill possessed the invention and that the limitations are described therein. As the specification and the original claims clearly delineate the limitations of the present invention, it is submitted that such a rejection would be improper.

Additionally, the MPEP states that the use of processes to define the invention may render the written description insufficient. However, "may" is a qualified term, thereby meaning that a method can be sufficient to satisfy the written description requirement. As the present application clearly illustrates the limitations of the invention in both the methods described and in the description of the claimed sequence in the specification and the original claims, it is submitted that such a basis for a rejection would not be well taken. Therefore, it is requested that the application be allowed.

Therefore, Applicant respectfully submits that the application is in condition for allowance and requests that all rejections be withdrawn.

In the event this paper is not timely filed, Applicant hereby petition for an appropriate extension of time. The fee for this extension may be charged to Applicant's Deposit Account No. 01-2300.

Please charge any fee deficiency or credit any overpayment to Deposit Account

No. 01-2300, referring to client-matter number 100564-09005.

Respectfully submitted,



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Attachments:      Marked Up Copy of Claims  
                            Petition for Extension of Time

### **MARKED UP COPY OF CLAIMS**

38. (thrice amended) A method for selecting OR or OL operator DNA sequences from lambdoid phages wherein said sequences have a different thermostability compared to a wild-type sequence with regard to binding a repressor, wherein said different thermostability results in repression of expression of a gene which is operatively linked to said DNA sequence until a temperature is reached that is 3 to 10° C higher than the temperature at which the wild type sequence is capable of repressing the expression of a gene operatively linked thereto, comprising

- (a) preparing a DNA cassette which contains a selection gene under the operative control of an expression control sequence comprising at least one OR or OL operator DNA sequence from a lambdoid phage and a promoter,
- (b) intentionally subjecting the operator DNA sequence to a [non-naturally occurring] mutagenesis, and
- (c) analyzing the operator DNA sequences to determine whether said sequences have a different thermostability as compared to a wild-type sequence with regard to binding a repressor.

46. (thrice amended) An OR or OL operator sequence from lambdoid phages which have an increased thermostability compared to a wild-type sequence with regard to binding of a temperature-sensitive  $\text{cl}$  repressor, wherein said increased thermostability results in repression of expression of a gene which is operatively linked to said DNA sequence until a temperature is reached that is 3 to 10° C higher than the temperature at which the wild type sequence is capable of repressing the expression of a gene operatively linked thereto, and wherein said sequences are obtained by a method comprising

- (a) preparing a DNA cassette which contains a selection gene under the operative control of an expression control sequence comprising at least one OR or OL operator DNA sequence from a lambdoid phage and a promoter,
- (b) intentionally subjecting the operator DNA sequence to a [non-naturally occurring] mutagenesis, and
- (c) analyzing the operator DNA sequences to determine whether said sequences have a different thermostability as compared to a wild-type sequence with regard to binding a repressor.

69. (twice amended) [The] A bacterial cell [according to claim 67] comprising at least one copy of a nucleic acid, wherein said nucleic acid comprises (a) a first bacterial expression control sequence which contains an OR or OL operator sequence from a lambdoid phage and to which a first  $\text{cl}$  repressor from lambdoid phages can bind, in operative linkage with a sequence coding for a second repressor wherein the second repressor cannot bind to the first bacterial expression sequence and (b) a second



bacterial expression control sequence to which the second repressor can bind in operative linkage with a suicide gene, wherein said first bacterial expression control sequence is an operator sequence from a lambdoid phage wherein said sequence has a different thermostability compared to a wild-type sequence with regard to binding of a repressor wherein said different thermostability results in repression of expression of a gene which is operatively linked to said DNA sequence until a temperature is reached that is 3 to 10° C higher than the temperature at which the wild type sequence is capable of repressing the expression of a gene operatively linked thereto, and wherein said operator sequence is obtained by a method comprising

- (a) preparing a DNA cassette which contains a selection gene under the operative control of an expression control sequence comprising at least one OR or OL operator DNA sequence from a lambdoid phage and a promoter,
- (b) intentionally subjecting the operator DNA sequence to a [non-naturally occurring] mutagenesis, and
- (c) analyzing the operator DNA sequences to determine whether said sequences have a different thermostability as compared to a wild-type sequence with regard to binding a repressor.

70. (twice amended) [The] A bacterial cell [according to claim 67] comprising at least one copy of a nucleic acid, wherein said nucleic acid comprises (a) a first bacterial expression control sequence which contains an OR or OL operator sequence from a lambdoid phage and to which a first cl repressor from lambdoid phages can bind, in operative linkage with a sequence coding for a second repressor wherein the second repressor cannot bind to the first bacterial expression sequence and (b) a second

bacterial expression control to which the second repressor can bind in operative linkage with a suicide gene, further comprising (c) a third bacterial expression control sequence which contains a operator sequence in operative linkage with a suicide gene, wherein said operator sequence is from a lambdoid phage and wherein said operator sequence has a different thermostability compared to a wild-type sequence with regard to binding of a repressor, wherein said different thermostability results in repression of expression of a gene which is operatively linked to said DNA sequence until a temperature is reached that is 3 to 10° C higher than the temperature at which the wild type sequence is capable of repressing the expression of a gene operatively linked thereto, and wherein said operator sequence is obtained by a method comprising

- (a) preparing a DNA cassette which contains a selection gene under the operative control of an expression control sequence comprising at least one OR or OL operator DNA sequence from a lambdoid phage and a promoter,
- (b) intentionally subjecting the operator DNA sequence to a [non-naturally occurring] mutagenesis, and
- (c) analyzing the operator DNA sequences to determine whether said sequences have a different thermostability as compared to a wild-type sequence with regard to binding a repressor.